

THE LANCET

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30 September 1998

Dr MF Murray
AIDS Service
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USA

Dear Dr Murray

Many thanks for submitting your hypothesis on niacin and AIDS to The Lancet.

We discussed your paper at an editorial meeting in light of the opinions of our peer reviewers. As you will see, our referees had some major concerns. Decisions about the suitability of a paper are made by editorial consensus, taking into consideration the interest to our readership, and the quality and suitability of the many other papers we consider each week. I am sorry to inform you that your paper did not meet our threshold for publication.

I wish you the best of luck for your paper elsewhere. Thank you for thinking of The Lancet.

Yours sincerely

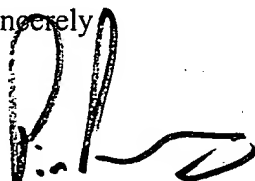

Dr Kelly Morris
Senior Editor

EXHIBIT 2

THE LANCET
MANUSCRIPT REVIEW

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Manuscript number: 08/ 8350
Authors: Murray MF
Reviewer number: 4241

Please give a frank account of the strengths and weaknesses of the article.

COMMENTS FOR AUTHORS:

The author proposes that niacin may act as an "AIDS preventive factor". By this he means that it will prevent progression from asymptomatic infection to symptomatic disease. It is however likely to be misconstrued as a factor which may prevent infection with HIV virus. The author should however be commended in trying to suggest an inexpensive treatment which may be used world-wide rather than just in the Western world.

Comments

- Nicotinamide acts as an inhibitor of HIV infection at millimolar concentrations. What are the concentrations of NAM achieved in vivo? For the hypothesis to be tenable the concentrations achieved in vivo should be equivalent to those required to inhibit HIV infection in vitro.
- HIV infected patients have been shown to have elevated niacin levels but decreased serum tryptophan and NAD levels. The latter are said to be reliable markers of niacin deficiency, but this is derived from studies carried out in young non-HIV infected men. With all the different metabolic changes occurring in HIV disease, I think one would have to be quite cautious in such an extrapolation. Clearly what is needed is a study in HIV patients which measures both extra- and intra-cellular concentrations of all the different vitamin compounds/metabolites, and related to viral load.
- Tryptophan deficiency is stated to be secondary to metabolic shunting towards NAD synthesis. However, it may also be due to increased protein synthesis as a result of the catabolic state, particularly in patients with a high viral load.
- The demonstration of improved clinical outcome with niacin (although only significant in one study) may have been due to confounding factors. In the study by Tang et al, benefit was also found with all the other vitamin B compounds. Should these also be given to patients, or should it only be niacin?

EXHIBIT 7

The article by Dr. Murray was read and while it presents some ideas that might have some modifying effects on HIV infection in some niacin-depleted individuals, the importance of this theory does not appear to be substantiated in any clinical trials. Furthermore, many HIV infected people take vitamin supplements and there have never been reports on any observed major effect on the clinical course except in the case of vitamin A. Many individuals and researchers have ideas that vitamins may provide some clinical benefit in HIV infection but the niacin theory needs much better substantiation and of course some kind of clinical trial. Thus, at this point the concept is so purely speculative that this paper should not have a high priority for publication in *The Lancet*.

EXHIBIT 2 }

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